

# Index

---

## A

---

- AAT ( $\alpha$ -1-antitrypsin), 501, 517  
Accord tobacco heater, 28*t*, 28–29, 71–72  
ACE (angiotensin-converting enzyme) inhibitors, 398  
acetaldehyde  
    in cigarette smoke, 59  
    effects of, 135–136  
    respiratory disease and, 49  
acrolein  
    in cigarette smoke, 59, 390  
    Eclipse, 32  
    pulmonary injury and, 465*t*  
    respiratory disease and, 49  
activated charcoal filters, 20, 66, 82  
acute tolerance, 140  
addiction. *See* nicotine addiction  
additives, 64–65  
adhesion molecules, 395  
adolescent tobacco use and dependence  
    chronic tolerance, 141  
    effects of nicotine, 136  
    epidemiology of, 180–182, 190  
    measuring, 180–185  
adult tobacco use and dependence  
    hematocrit levels, 401–402  
    prevalence of, 186–189, 187*t*–188*t*, 189*f*, 190*t*–191*t*  
        by dose, duration, and subpopulations, 187*t*–188*t*, 189–191  
    psychiatric comorbidity, 191–193  
    summary and future directions, 193–194  
Advance cigarettes, 24, 25*t*, 72  
advertising, 689  
aerosols, particle-size distribution in, 70–71  
affective dimension/symptoms, 197–198, 200, 202*f*  
A549 cell line, 82  
African heritage, people with  
    cigarette marketing to, 19–20  
    coronary heart disease in, 385  
    nicotine dependence in, prevalence of, 190–191  
    *PI\*Z* alleles, 501  
    smoking topography, 68  
AGT. *See* *O*<sup>6</sup>-alkylguanine–DNA alkyltransferase  
airway epithelial cells  
     $\beta$ -adrenergic receptors, 313  
    nicotinic acetylcholine receptors, 312–314  
    other receptors, 313–314  
airway obstruction, 470, 471*f*, 503  
airway remodeling, 481–482  
AKT (protein kinase B), 311, 314–315  
Alaska Natives, 186  
Albany Study, 385  
alcohol abuse/dependence  
    baclofen and, 153  
    nicotine dependence and, 162, 191–193  
    as relapse risk factor, 198  
alcohol intake  
    as relapse risk factor, 203  
    as smoking reinforcement, 143  
    synergistic interactions in tobacco carcinogenesis, 321–322  
aldehyde compounds, 58–60  
aldehydes, 59, 251  
alkylating agents, 258  
Allen & Ginter Company, 18  
allergic reactions, 96  
all-*trans* retinoic acid, 517  
 $\alpha$ -1-antitrypsin (AAT), 501, 517  
 $\alpha$ -tocopherol, 89  
alveolar macrophages, 516  
American Academy of Family Physicians, 687  
American Academy of Pediatrics, 687  
American College of Physicians, 687  
American Correctional Association, 686  
American Indians, smoking prevalence in, 186  
American Medical Association, 687  
American Nursing Association, 687  
American Tobacco Company, 18–19  
amino acid deficiencies, 626  
4-aminobiphenyl (4-ABP), 259, 260*f*, 261  
4-aminobiphenyl-C8-deoxyguanosine, 297  
amphetamines, 143  
angiogenesis, pathologic, 397–398  
angiotensin-converting enzyme (ACE) inhibitors, 398  
anhedonia, 155  
animal studies  
    cytotoxicity, 83–88, 86*t*  
    emphysema, 517–518, 518*t*  
    inhalation, 85–88, 86*t*  
    oxidative stress, 491, 492*t*–493*t*, 493  
    skin-painting, 83–85  
    usefulness of, 83  
antidepressant drugs, 158–159  
antimony, 61  
antioxidants, 485–487, 486*f*. *See also specific substance*  
antioxidant vitamins, 397  
antiprotease-protease imbalance, 498, 521  
antiprotease therapy, 519, 519*t*

---

**Note:** Page numbers followed by *t* and *f* denote tables and figures, respectively.

antipsychotic drugs, 158–159  
 anxiety disorders, 192  
 anxiolytic effects, 150  
 aortic aneurysm, 386  
 apolipoproteins, 412  
 apoptosis, 308  
   antiapoptotic proteins and, 310–312  
     in COPD, 499  
     cytotoxicity of tobacco smoke, 82  
     in emphysema, 519–520  
     proapoptotic proteins and, 308–310, 309f  
     regulators of, 308  
 apurinic/apyrimidinic sites, 297  
 Ariva “cigalett bits,” 26–27, 27t  
 aromatic amines, 59  
   as biomarkers, 254, 255f, 256, 269  
   in cigarette smoke, 61–62, 62f, 78, 251  
 arsenic  
   cardiovascular disease and, 49  
   reproductive and developmental effects of, 615  
   in tobacco smoke, 61, 613  
 asbestos, 20, 322  
 Asian heritage, people with  
   coronary heart disease in, 385  
   *PI\*Z* alleles, 501  
   smoking prevalence in, 186  
 aspirin, 400, 404  
 associative learning processes, 144–145, 145f  
 asthma, 465t  
 atherosclerosis, 395  
 atorvastatin, 404  
 attitudinal influences, 196, 200–201  
 autoimmune disorders, 609  
 automated cigarette-making machine, 18

## B

baclofen, 152–153  
 BAL (bronchoalveolar lavage), 516  
 base excision repair  
   overview of, 277t, 277–278, 279f  
   polymorphisms in, 288–289  
   protecting against mutagenicity and carcinogenicity, 278  
   substrate specificity, 278  
 Bayley Scales of Infant Development, 567  
 B cells, 478f, 479  
 BCL-2 family proteins, 309, 309f  
 beer, nicotine, 30, 31t  
 benzene  
   as biomarker, 255f, 257  
   in cigarette smoke, 251  
   metabolism of, 261  
 benzo[a]pyrene, 259, 260f  
 benzo[a]pyrene-7,8-diol-9,10-epoxide-*N*<sup>2</sup>-deoxyguanine  
   stereoisomers, 297

beryllium, 613  
 β-adrenergic receptors, 313  
 beta-carotene, 487  
 bidis, 385  
 bile, 76  
 biomarkers. *See also specific biomarker*  
   of addiction potential, 681, 682t  
   animal bioassays, 83–88, 86t, 90–96  
   of biologically effective dose, 74–76  
   blood, 258  
   breath, 258  
   of cancer risk, 677, 677f  
   cardiovascular, 88–90, 415–418, 416t–417t  
   cerebrovascular, 88–90  
   cytotoxicity, 81–99, 86t  
   DNA adducts, 266–269, 267t  
   endocrine system, 97–99  
   of exposure, 73–75  
   genotoxicity, 77–81  
   immune system, 96–97  
   of oxidative stress, 497  
   of potential harm, 74, 76–77  
   reproductive and developmental, 93–96  
   respiratory, 90–93  
   as risk assessment tools, 73  
   types of, 73–77  
   urinary, 254–258, 255f  
 birth defects  
   carbon monoxide and, 611  
   maternal and neonatal genetic polymorphisms, 626–629, 628t–629t  
   maternal smoking and, 565–566, 568t–571t, 572t–573t, 574t–581t, 636–637  
 birth weight  
   infant survival and, 565  
   low, 564, 611, 614  
   maternal and neonatal genetic polymorphisms, 629–631, 630t–631t  
   polycyclic aromatic hydrocarbons and, 616t–621t, 623  
   secondhand smoke and, 564, 630t–631t, 631  
 bladder cancer  
   biomarkers, 76  
   carcinogen-metabolizing gene polymorphisms, 269, 274  
   cytogenic effects of tobacco smoke, 80  
   DNA adducts and, 268  
   gene promoter hypermethylation, 318  
   specific carcinogens related to, 323t, 324  
   *TP53* gene mutations, 307  
 blood  
   alterations in, 399–403, 400f (*See also* thrombogenic effects)  
   biomarkers in, 75, 258  
   DNA adducts in, 268–269  
   hyperviscosity, carbon monoxide and, 611  
 blood pressure, 89–90, 392  
   maternal (*See* maternal blood pressure)  
 blood vessels, alterations in, 404–405

body weight. *See also* birth weight  
 cigarette smoke exposure and, 98–99  
 COPD and, 499–500  
 reproductive and developmental studies, 94  
 Bonsack, James, 18  
 Boston Early-Onset COPD Study, 503, 505  
 breast cancer, 268, 673  
 breath biomarkers, 258  
 British Doctors' Study, 675–676, 676f  
 bronchitis, chronic, 465t, 467–469, 468f, 503  
 bronchoalveolar lavage (BAL), 516  
 Brundtland, Gro Harlem, 680  
 bupropion  
     cardiovascular disease and, 419, 422t–423t, 425  
     dopamine transmission and, 156  
     for nicotine addiction, 148, 154, 156, 159, 200, 674  
     pharmacogenetics, 178  
     pregnancy and, 632  
 Bureau of Alcohol, Tobacco, Firearms and Explosives, 689  
 buspirone, 159  
 1,3-butadiene, 49  
     biomarker of carcinogens, 255f, 257  
     cancer risk, 49  
     carcinogen in cigarette smoke, 251  
     metabolic activation, 261

## C

cachexia, 499–500  
 cadmium  
     as biomarker, 258  
     placental levels of, 77  
     pulmonary injury and, 465t  
     reproductive and developmental effects, 614–615  
     in tobacco smoke, 60–61, 251, 390, 613  
 California Birth Defects Monitoring Program, 627  
 Cambridge glass filter, 50  
 cancer. *See also* carcinogen(s); *specific type of cancer*  
     activation of cell-surface receptors in, 312–316  
     cell-cycle control in, 318–320  
     chromosome instability and loss in, 295t, 298t, 298–301  
     conclusions, 10, 328  
     DNA adducts (*See* DNA adducts)  
     DNA repair (*See* DNA repair)  
     evidence summary, 326–327  
     future research recommendations, 683  
     gene promoter hypermethylation in, 316–318  
     pathways of causation, 249–250, 250f  
     signal transduction in, 308–312, 309f  
     smoking cessation and, 250  
 Cancer Prevention Study II, 379–380, 380f, 381f  
 candidate gene studies, 162  
     dopaminergic and serotonergic systems, 165, 168, 174t–175t  
     nicotine metabolism, 165–169, 166t–169t  
     nicotinic receptors, 165, 168t–169t  
     smoking behavior, 176t–177t

carbon dioxide, 59  
 carbon filters, 20, 66, 82  
 carbon-heated “smoking” devices, 22  
 carbon monoxide (CO)  
     as biomarker, 497  
     blood hyperviscosity and, 611  
     cardiovascular disease and, 391  
     in cigarette smoke, 59, 388–390  
     Eclipse, 28, 28t, 29  
     fetal exposure to, 611, 637  
     preeclampsia and, 611–612  
     tobacco heating systems, 72  
     toxicity of, 612  
 carbonyl compounds, 59  
 carboxyhemoglobin, 389, 389f  
 carcinogen(s). *See also specific substance*  
     biomarkers, 254–259, 255f  
     as causes of specific cancers, 322–324, 323t  
     in cigarette smoke, 251–254, 252t–253t, 320–321  
     enzymology of, 261–265  
     immunosuppressive changes, 97  
     metabolic activation and detoxification, 249, 252t–253t, 259–261, 260f  
 carcinogenesis  
     broadened research on, 6–7  
     synergistic interactions in, 321–322  
 carcinogen-metabolizing genes, 269–275, 270t  
 cardiomegaly, 90  
 cardiovascular diseases, 379–386. *See also specific disease*  
     animal studies, 88–90  
     biomarkers, 76, 415–418, 416t–417t, 676  
     chemicals likely to cause, 49, 388–390, 389f  
     conclusions, 10–11, 432  
     dose-response relationship, 382f  
     duration of smoking and, 383t, 384t  
     endothelial changes in, 394–398  
     evidence summary, 432  
     future research recommendations, 683–684  
     harm reduction, 426–431, 464t  
     hemodynamics in, 392–394  
     inflammation in, 406–407  
     lipid abnormalities in, 411–415  
     pathophysiology of, 4, 5f, 379, 388–391, 389f, 391f  
     risk assessment, 379–380, 380f, 381f  
     secondhand tobacco smoke and, 387–388  
     smokeless tobacco and, 387  
     smoking cessation and, 419–426, 421t–423t  
 cardiovascular malformations, 566, 572t–573t  
 Carlton cigarettes, 70  
 “casing” solution, 64  
 catalase, 486, 486f  
 catecholamines, 98  
 causal inferences, 3, 3t  
 CCND1 gene, 318–319  
 CDC. *See* Centers for Disease Control and Prevention  
 CD4 helper T cells, 478f, 479  
 CDKN2A (P16) tumor-suppressor gene, 316  
 cell-cycle control, 318–320

- cell-derived oxidants, 488
- Centers for Disease Control and Prevention (CDC)
  - lung cancer and COPD study, 463
  - Office on Smoking and Health, 8
  - research recommendations, 687
  - tobacco control measures, 686, 690–691
- cerebrovascular diseases, 88–90. *See also specific disease*
- cervical cancer, 323*t*, 324
  - DNA adducts, 268
  - genotoxic effects of tobacco smoke, 79
- cervical mucus biomarkers, 75
- characterized adducts, 266, 267*t*
- chemistry. *See also specific substance*
  - additives, 64–65
  - aromatic amines, 61–62, 62*f*
  - conclusions, 9, 101
  - delivery of chemicals to smokers, 65–71
  - heavy metals, 60–61
  - heterocyclic amines, 63*f*, 63–64
  - modified tobacco products, 71–73
  - nicotine and free nicotine, 51–54, 52*f*, 53*f*
  - N*-nitrosamines, 54–57, 55*f*
  - phases of tobacco smoke, 50–51
  - polycyclic aromatic hydrocarbons, 57, 58*f*
  - volatile and aldehyde compounds, 58–60
- chewing gum. *See* nicotine gum
- children of smokers, 79
- chlorisondamine, 156
- cholesterol, 414. *See also* lipid levels
- CHRNA4* gene, 165, 168*t*–169*t*
- CHRNA7* gene, 165, 168*t*–169*t*
- chromium, 61, 613–614
- chromosomal instability and loss, 79–80
  - in lung cancer, 298
  - oncogene activation and, 295*t*, 299–301
  - tumor-suppressor genes, 298*t*, 298–299, 301
- chronic bronchitis, 465*t*, 467–469, 468*f*, 503
- chronic obstructive pulmonary disease (COPD), 465*t*, 469, 470*f*
  - genetic associations, 505–512, 506*t*–513*t*
  - phenotype linkage analysis, 503–505, 504*t*
  - mortality, 463, 677–678
  - oxidative stress and, 497–500
  - pulmonary hypertension and, 473–475
  - severity classifications, 469, 470*f*
- chronic tolerance, 140–141
- cigarette(s). *See also specific type or brand of cigarette*
  - definition of, 16–18
  - design of, 18–21
- cigarette-like products, 17, 27–29, 28*t*
- cigarette modifications. *See also* modified tobacco products
  - conclusions, 9, 36
  - consequences of, 20–22
  - consumer perceptions and use of, 15
  - influences on, 18–20
  - potential reduced-exposure products (*See* potential reduced-exposure products)
  - potential risks and benefits, 32–34
  - product evaluation, 15, 23
  - purpose of, 15
- cigarette paper, 66
- cigarette smoke
  - activation of cell-surface receptors in airway epithelial cells by, 312–315
  - carcinogens in (*See* carcinogen(s))
  - constituents of (*See* chemistry; *specific substance*)
  - emphysema models, 517–519
  - formation of, 67
  - genotoxicity of, 77–78
  - oxidants, 488
- cigarette substitutes, 17. *See also* cigarette modifications; modified tobacco products
- cigarette taxes, 680
- cigars, 386
- ciliotoxicity assays, 81
- circulating proteins, 403
- classic conditioning, 144–145, 145*f*
- cleft lip/cleft palate
  - genetic polymorphisms, 626–629, 628*t*–629*t*
  - maternal smoking and, 565–566, 568*t*–571*t*
- clonidine, 156, 419, 426, 632
- cloud motion, 71
- clozapine, 160
- clubfoot, 566, 576*t*–579*t*
- CO. *See* carbon monoxide
- cobalt, 61
- cocaine, 143, 153
- Cochrane Database of Systematic Reviews, 419
- cognitive domain, 142, 196, 200–201
- “coherence of the association,” 4, 6, 6*t*
- collagenase, 519
- comet assay, 287–288
- Committee to Assess the Science Base for Tobacco Harm Reduction, 674
- “compensatory smoking,” 19, 21
- Composite International Diagnostic Interview-Substance Abuse Module, 186
- conclusions, 8–9, 101
  - cancer, 10, 328
  - cardiovascular diseases, 10–11, 432
  - cigarette modifications and substitutes, 9, 36
  - cigarette smoke chemistry and toxicology, 9, 101
  - nicotine addiction, 9–10, 207
  - reproductive and developmental effects, 11, 638
  - respiratory diseases, 11, 463, 464*t*, 522
- conditioned stimulus in nicotine addiction, 144–145, 145*f*
- congenital lobar form of emphysema, 473
- consumer education, 691
- consumer perceptions, 15, 32–33
- COPD. *See* chronic obstructive pulmonary disease
- Copenhagen City Heart Study, 469
- coronary blood flow, 392–394
- coronary heart disease, 676
  - animal studies, 90
  - cigarettes smoked per day, 380–383, 382*f*

- duration of smoking and, 383*t*, 384*t*
- race and ethnicity, 385
- secondhand smoke, 673
- smoking cessation, 383–384
- women, 384
- cotinine, 77, 136, 382
- counseling, 420, 421*t*, 422
- COX-1 (cyclooxygenase-1), 312
- COX-2 (cyclooxygenase-2), 312, 314, 390
- craniosynostosis, 566, 574*t*–575*t*, 580*t*–581*t*
- craving, 146–148, 199, 199*f*
- C-reactive protein, 403
- CREB (cyclic adenosine monophosphate-response element binding protein), 158
- cresols, 49
- cross-complementation group 1 for excision repair (*XRCC1*), 288–290
- cryptorchidism, 566, 574*t*–575*t*, 578*t*–579*t*
- cue-provoked craving, 146–148
- curing process
  - nitrosamine formation, 54–55
  - STARCURE™ tobacco, 24, 27
  - TSNAs, 72
- cyanide, 49
- cyclic adenosine monophosphate-response element binding protein (CREB), 158
- cyclooxygenase-1 (COX-1), 312
- cyclooxygenase-2 (COX-2), 312, 314, 390
- CYP1A1* gene, 270*t*, 270–273
- CYP2A6* gene, 165, 166*t*–169*t*, 168
- CYP2A13* gene, 270*t*, 271
- CYP2B6* gene, 178
- CYP2E1* gene, 270*t*, 271
- cytochrome P-450 enzymes, 261–262
- cytogenic effects, 78–81
- cytoplasmic kinase, 314–315
- cytotoxicity
  - animal studies, 83–90, 86*t*
  - body weight, 98–99
  - cardiovascular system, 88–90
  - cerebrovascular system, 88–90
  - endocrine system, 97–99
  - immune system, 96–97
  - reproductive and developmental, 93–96
  - respiratory system, 90–93
  - testing for, 81–83

## D

- deaths. *See* mortality
- decision-tree analyses, 197
- demographic variables, 196–197
- denicotinized tobacco, 16–17, 22
- Department of Health and Human Services, 687, 689

- depression
  - major, 192–193
  - nicotine dependence and, 159
  - as relapse risk factor, 142, 198
  - smoking prevalence and, 158
- dermal application of cigarette smoke condensate, 83–85
- desmosine, 517
- developmental effects. *See* birth defects; fetal effects; reproductive and developmental effects
- developmental immunotoxicity, 616*t*–621*t*, 623–624
- diabetes, 407–411
  - insulin resistance, 408–409
  - macrovascular complications, 410
  - metabolic control, 408
  - microvascular complications, 409–410
  - pathophysiological mechanisms, 411
  - peripheral arterial disease, 386
  - risk for, 407–408
  - summary, 411
- Diabetes Control and Complications Trial, 410
- Diagnostic and Statistical Manual, Third Edition Revised (DSM-III-R)*, 186, 189
- Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*
  - adolescent nicotine dependence, 180–181
  - nicotine dependence diagnostic criteria, 130, 130*t*, 133*t*, 186
- disease causation schema, 3–4, 4*f*
- distal acinar emphysema, 473
- distress tolerance, 198
- DNA adducts
  - biomarkers, 75, 266–269, 267*t*
  - cardiovascular studies, 90
  - characterized, 266, 267*t*
  - conversion to mutations, 292–297, 294*f*, 294*t*
  - formation of, 249–250
  - genotoxicity assessment, 297
  - in other tissues, 268–269
  - protein adducts as surrogates for, 269
  - repair of, 276–283
    - base excision, 276–283, 277*t*, 277–278, 279*f*
    - double-strand break, 283, 284*f*, 285*f*
    - mismatch, 282*f*, 282–283
    - nucleotide excision, 278–282, 280*f*, 281*t*
    - O*<sup>6</sup>-alkylguanine–DNA alkyltransferase, 276
  - summary, 269
  - uncharacterized, 268
- DNA damage, 78, 80. *See also* chromosomal instability and loss
- DNA repair
  - base excision, 288–289
  - comet assay, 287–288
  - double-strand break, 292
  - 8-oxoguanine DNA glycosylase, 287
  - functional assays, 285, 287
  - genes and pathways involved, 283, 286*t*
  - genotype-phenotype correlations, 291–292
  - mutagen sensitivity assays, 287

nucleotide excision, 289–291  
*O*<sup>6</sup>-alkylguanine–DNA alkyltransferase, 288  
*OGG1* gene, 289  
 summary, 292  
 dopamine  
   neurochemical correlates of nicotine withdrawal, 156  
   nicotine replacement therapy, 169, 176  
   nicotinic acetylcholine receptors, 150  
   nornicotine, 135–136  
 dopamine receptor D2 (*DRD2*), 165, 170*t*–173*t*, 178  
 dopaminergic systems, 165, 170*t*–173*t*  
 dose-response relationship  
   cigarettes smoked per day, 381–383, 382*f*  
   ectopic pregnancy and, 560  
   emphysema and, 472, 472*f*  
   harm reduction, 431  
   menopause and, 551  
   nicotine dependence and, 189  
 double-strand break repair, 283, 284*f*, 285*f*, 292  
 Down syndrome, 566, 574*t*–577*t*  
*DRD2* (dopamine receptor D2), 165, 170*t*–173*t*, 178  
 drug dependence, 192–193  
*DSM-III-R* (*Diagnostic and Statistical Manual, Third Edition Revised*), 186, 189  
*DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*)  
   adolescent nicotine dependence, 180–181  
   nicotine dependence diagnostic criteria, 130, 130*t*, 133*t*, 186  
 “dual product use,” 33  
 Duke, James “Buck,” 18  
 Dunn, William, 17  
 dye exclusion assay, 81

## E

ECigarettes, 31*t*  
 Eclipse tobacco heater, 20, 28, 28*t*, 32, 71–72  
 ectopic pregnancy, 557, 560, 634–635  
 education, consumer, 691  
 educational status, 186  
*EGFR* gene, 300*t*, 300–301, 313–314  
 elastases, 514–515, 518–519  
 “elastic” cigarettes, 69  
 elastin-derived peptides, 517  
 electronic nicotine delivery systems (ENDS), 17–18, 30, 31*t*  
 emergent processes, 195, 198–201, 199*f*–202*f*  
 emphysema  
   animal studies, 91–92  
   centrilobular, 472–473, 473*f*, 474*f*, 475*f*  
   congenital lobar, 473  
   defined, 465*t*, 471–472, 513  
   distal acinar, 473  
   dose-response relationship, 472, 472*f*  
   mantle, 473  
   oxidative stress and, 493  
   panacinar, 472–473, 475*f*

paracitricial, 473  
 paraseptal, 473  
 pathogenesis of, 476*f*, 513–515, 514*f*  
   proteases and, 515–520, 518*t*  
   summary, 520  
   unilateral form (McLeod syndrome), 473  
*Ending the Tobacco Problem: A Blueprint for the Nation*, 678, 686–690  
 endocannabinoid system, 154, 156  
 endocrine system, 580–581  
   disruption by PAHs, 624  
   in healthy men, 587, 588*t*–591*t*  
   pathophysiological mechanisms, 581–587, 584*t*–587*t*, 588*t*–591*t*  
   postnatal changes in, 98  
   in pregnant women, 583  
   in premenopausal women, 581–586, 584*t*–587*t*  
   studies of, 97–99  
 endothelial progenitor cells, 394  
 endothelium  
   cardiovascular, 89–90, 393–394, 415  
   dysfunction, 393–395, 415  
   nitric oxide and, 396  
   pathologic angiogenesis, 397–398  
   regeneration of, 394  
   summary, 398  
 endothelium-dependent vasodilation, 396–397  
 ENDS (electronic nicotine delivery systems), 17–18, 30, 31*f*  
 environment  
   nicotine self-administration and, 146–148  
   as relapse risk factor, 197, 199, 200*f*  
 Environmental Protection Agency (EPA), 7  
 enzyme antioxidants, 485–487, 486*f*. *See also specific substance*  
 enzymology of carcinogen metabolism, 261–265  
 EPA (Environmental Protection Agency), 7  
 epidermal growth factor receptor, 311  
 epigenetics, 316  
 epithelial injury, 491, 496  
 epithelial lining fluid, antioxidants in, 486–487  
 epoxide hydrolases, 262–263  
 ERBB receptors, 313  
 ERKs (extracellular signal-regulated kinases), 315  
 erlotinib, 301  
 esophageal cancer, 307, 322, 323*t*  
 ethnicity, 385. *See also specific ethnic group*  
 ethylene oxide, 251, 259, 260*f*  
 eugenol, 64  
 euglycemic hyperinsulinemic clamp technique, 408  
 European Commission, 26  
 European heritage, people with  
   AAT deficiency, 501  
   coronary heart disease, 385  
   nicotine dependence prevalence, 190–191  
   smoking topography, 68  
 evidence summary, 4, 6*t*, 6–7  
   cancer, 326–327  
   cardiovascular diseases, 432  
   genetics, 161, 521



- nicotine addiction, 204–206
- pulmonary diseases, 520–521
- reproductive and developmental effects, 634–637
- Evolution, 30, 31*t*
- Exalt, 26, 27*t*, 27
- exhaled air biomarkers, 74
- exocyclic etheno adducts, 297
- expanded tobacco, 84, 88
- extracellular signal-regulated kinases (ERKs), 315

## F

- Fagerström Test for Nicotine Dependence (FTND), 130, 131*t*, 133*t*
- Fagerström Tolerance Questionnaire (FTQ)
  - adolescent nicotine dependence, 180–181
  - severity of dependence, 130, 131*t*, 133*t*
- Family Smoking Prevention and Tobacco Control Act of 2009*, 23, 679–680
- FDA. *See* Food and Drug Administration
- Federal Cigarette Labeling and Advertising Act*, 16
- Federal Trade Commission (FTC)
  - tar and nicotine yields, 19
  - marketing statements about, 22
  - tar delivery claims, advertising ban on, 18
  - testing conditions, 49
  - test methods, 21–22
- fertility, 551–552. *See also* reproductive and developmental effects
  - causal links, 634
  - female, 552
  - male, 552–553, 554*t*–557*t*
- fetal effects
  - animal studies, 94–95
  - carbon monoxide and, 611
  - cardiovascular, 594, 595*t*–600*t*, 596–602
  - growth, 564, 635–636
  - organogenesis, 603–609, 604*t*–608*t*
  - pathophysiological mechanisms, 602–609
- fetal heart rate
  - acute effects on, 597*t*–600*t*, 601
  - maternal smoking abstinence and, 596, 600
  - variability in, 595*t*, 597*t*–600*t*, 601
- fibrinogen, 403
- 51 nicotine delivery system, 31*t*
- filter tips
  - asbestos in, 20
  - delivery of chemicals into smoke, 66–67
  - glass fibers in, 20, 32, 50
  - heavy metals and, 61
  - marketing strategy, 20–21
  - nitrosamine removal, 56
  - percentage of cigarette market, 18–19
  - risks caused by, 19–20
  - ventilated, 20, 22, 67, 69

- Final Tobacco Rule (1996), 16–17
- Firebreak, 27*t*, 27
- “599 list,” 64
- flavorings, 64–65
- flow-mediated arterial vasodilation, 415
- fluoxetine, 159
- fluvastatin, 404
- folate, 80
- Food and Drug Administration (FDA)
  - Final Tobacco Rule (1996), 16–17
  - new regulatory authority, 23
  - regulation of tobacco products, 690
  - regulatory authority, increasing, 688–690
  - tobacco harm reduction, scientific base for, 16
  - food intake, smoking abstinence and, 153
- formaldehyde, 59, 465*t*
- Framework Convention on Tobacco Control, 680
- Framingham Heart Study
  - peripheral arterial disease, 386
  - phenotype linkage analysis, 504–505
  - stroke, 385
  - sudden death, 385
- free fatty acids, 413
- free nicotine, 52, 53*f*
- FTC. *See* Federal Trade Commission
- FTND (Fagerström Test for Nicotine Dependence), 130, 131*t*, 133*t*
- FTQ (Fagerström Tolerance Questionnaire)
  - adolescent nicotine dependence, 180–181
  - severity of dependence, 130, 131*t*, 133*t*
- functional magnetic resonance imaging, 158
- future vision
  - concluding remarks, 680
  - Ending the Tobacco Problem: A Blueprint for the Nation*, 686–690
  - global tobacco epidemic, 673–678, 676*f*, 677*f*
  - ending, 678–680
  - President’s Cancer Panel recommendations, 690–692
  - research recommendations, 681–686, 682*t*

## G

- γ-aminobutyric acid (GABA), 152–153, 157
- γ-glutamyltranspeptidase, 487
- gas phase of tobacco smoke
  - carcinogenic effects, 321
  - constituents in, 51
  - defined, 50
  - oxidants in, 488
  - volatile nitrosamines in, 55
- gastroschisis, 566, 578*t*–579*t*
- gefitinib, 301
- gender factors. *See* men; women
- gene mutations, 249–250. *See also* chromosomal instability and loss; *specific gene*

gene profiling, 517  
 gene promoter hypermethylation, 316–318  
 gene silencing, 317  
 genetic polymorphisms. *See also specific gene*  
   bladder cancer, 269  
   cleft lip/cleft palate, 626–627, 628*t*–629*t*  
   DNA repair, 288–291  
   lung cancer, 269–275, 270*t*  
   maternal and neonatal, 626–631, 628*t*–631*t*  
   microsomal epoxide hydrolase, 274–275  
 genetics. *See also specific disease*  
   pharmacogenetics, 169, 176–179  
   of smoking behavior, 161–169, 163*t*–164*t*, 166*t*–169*t*, 170*t*–177*t*  
   summary and future directions, 179  
 genotoxicity  
   children of smokers, 79  
   cigarette smoke condensate, 77–78  
   DNA adduct assessment, 297  
   studies of, 78–81  
 genotype-phenotype correlations, 291–292  
 glass fibers, 20, 32, 50  
 global genomic nucleotide excision repair, 278–281, 280*f*, 281, 281*t*  
 Global Initiative for Chronic Obstructive Lung Disease (GOLD), 469, 470*f*  
 glucose levels, 97–98, 418  
 glutamate, 150–152, 157  
 glutathione-S-transferases (GSTs), 263–264, 487  
 glutathione (GSH) system, 486–487  
 glycosylases, 277, 277*t*, 279*f*  
 GOLD (Global Initiative for Chronic Obstructive Lung Disease), 469  
 GothiaTek manufacturing process, 26  
 growth control, loss of mechanisms for, 308–320, 309*f*  
 GSH (glutathione) system, 486–487  
*GSTM1* gene, 270*t*, 272–273  
*GSTP1* gene, 270*t*, 273  
 GSTs (glutathione-S-transferases), 263–264, 487  
*GSTT1* gene, 270*t*, 273  
 G→T transversions, 303–305, 307  
*Guidelines for Carcinogen Risk Assessment* (EPA), 7  
 gum. *See* nicotine gum

## H

harm reduction  
   benefits of, 426  
   defined, 71  
   exposure reduction methods, 431  
   implications for, 431  
   nicotine replacement therapy, 430  
   proposed methods for, 674–675  
   reduced smoking, 426–431, 428*t*–429*t*  
   summary, 431

head cancers, 318  
 Health Professionals Follow-Up Study, 407  
 heart rate, 392  
   fetal (*See* fetal heart rate)  
   maternal (*See* maternal heart rate)  
 hematocrit, 401–402  
 hemodynamic effects, 392–394  
 heritability. *See* genetics  
*HER-2/NEU* gene, 300*t*, 300–301  
 heterocyclic amine protein pyrolysate products, 78  
 heterocyclic amines, 63*f*, 63–64  
 heterocyclic aromatic amines, 256  
 Hispanic heritage, people with, 385  
 homologous DNA recombination, 283, 284*f*  
 Honolulu Heart Program, 385  
 Hooked on Nicotine Checklist, 180  
 host-cell reactivation assay, 285  
 HPRT (hypoxanthine phosphoribosyl transferase) mutations, 78–79  
*5HTT* gene, 168, 174*t*–175*t*  
 hydrocarbons, 59–60  
 hydrogen cyanide, 465*t*  
 1-hydroxypyrene, 254, 255*f*, 415  
 hypercoagulable state, 415  
 hypospadias, 566, 574*t*–579*t*  
 hypoxanthine phosphoribosyl transferase (HPRT) mutations, 78–79  
 hypoxia, 611

## I

IARC. *See* International Agency for Research on Cancer  
*ICD-10 (International Classification of Diseases, 10th Revision)*, 130, 130*t*, 186  
 iCig, 31*t*  
 ilomastat, 519, 519*t*  
 imaging studies, 136, 158  
 immune system, 476*f*, 477–478  
   adaptive response, 476*f*, 478*f*, 478–479, 480*f*  
   carcinogens and cancer, 324  
   pathophysiological mechanisms, 609–610  
   reproductive and developmental effects, 609–610  
   studies of, 96–97  
 immunosuppression  
   carcinogens and cancer, 324  
   reproductive and developmental effects, 609–610  
   studies of, 96–97  
 implications  
   harm reduction, 431  
   pulmonary diseases, 522  
   reproductive and developmental effects of cigarette smoking, 632–634  
 “incentive amplification,” 145  
 income level, 186



inductive plethysmography, 70  
 infant mortality, 564–565, 633  
 inflammation  
     cardiovascular diseases, 406–407, 415, 418  
     oxidative stress and, 491, 496  
 inhalation patterns, 70  
 inhalation studies, 85–88, 86*t*  
 Institute of Medicine (IOM)  
     biomarker of exposure definition, 74  
     cigarette substitutes, 33–34  
     *Ending the Tobacco Problem: A Blueprint for the Nation*, 678, 686–690  
     tobacco harm reduction, 15–16, 674–675  
 insulin dosage, 408  
 insulin resistance  
     cardiovascular biomarkers, 418  
     diabetes and, 408–409  
     lipolysis inhibitors, 414  
 Insulin Resistance Atherosclerosis Study, 407  
 intellectual abilities and maternal smoking, 567, 580  
 INTERHEART study, 385, 387, 431  
 International Agency for Research on Cancer (IARC)  
     carcinogenesis mechanisms, 6–7  
     carcinogens, 29, 251, 252*t*–253*t*  
     tobacco harm reduction, 16  
*International Classification of Diseases, 10th Revision (ICD-10)*, 130, 130*t*, 186  
 International Collaborative Study on Genetic Susceptibility to Environmental Carcinogens, 271, 273  
 International Organization for Standardization, 49  
 intrauterine growth retardation, 629–631, 630*t*–631*t*  
 in vitro studies  
     AGT, 276  
     cytotoxicity, 82–83  
     oxidative stress, 489–491, 490*t*  
 IOM. *See* Institute of Medicine  
 IPCO Creamy Snuff, 30  
 ischemic myocardium, 393  
 isoprostanes, 401

## J

Jenkins Act, 689  
 Joint Commission on the Accreditation of Healthcare Organizations (JCAHO), 686

## K

kenacid blue binding assay, 81  
 ketones, 59  
 Koch's postulates, 6  
*KRAS* gene, 80–81

## L

lactate dehydrogenase release assay, 81  
 laryngeal cancer, 268, 307, 322, 323*t*  
 lead  
     reproductive and developmental effects, 613–615  
     in tobacco smoke, 60–61, 390  
 learning and conditioning  
     environmental context, 146–148  
     negative reinforcement, 146  
     positive reinforcement, 145–146  
     secondary reinforcement, 144–145, 145*f*  
     summary and future directions, 148  
 Legacy Tobacco Documents Library, 21  
 leukemia, 80, 323*t*, 324  
 leukocytes, 402–403  
 Liebowitz, Jon, 22  
 lifestyle  
     healthy, promoting, 690–692  
     as relapse risk factor, 196–197  
 limb deficiency defects, 566, 574*t*–579*t*  
 linkage studies  
     COPD phenotypes, 503–505, 504*t*  
     smoking behavior, 162, 163*t*–164*t*, 164  
 lip contact, 69  
 lipid abnormalities  
     composition, 412  
     effects of smoking cessation on, 414  
     epidemiology of, 411–412  
     free fatty acid metabolism, 413  
     lipid transfer enzymes, 412  
     oxidized lipoproteins, 412–413  
     postprandial changes, 413  
     reverse cholesterol transport, 414  
     summary, 415  
     therapeutic implications of, 414  
 lipid levels, 89, 418  
 lipid peroxides, 497  
 lipolysis inhibitors, 414  
 lipoprotein-associated lipid transfer enzymes, 412  
 lipoproteins, 412–413  
 liver cancer, 322, 323*t*  
 lollipops, nicotine, 30, 31*t*  
 lotion, nicotine, 30, 31*t*  
 low birth weight, 564, 611, 614  
 low-nicotine cigarettes, 24–26, 25*t*, 73  
 low-tar cigarettes, 386  
 lozenges, nicotine, 22, 26–27, 27*t*, 31  
 luciferase host-cell reactivation assay, 285  
 lung cancer  
     adenocarcinoma, 22  
     cytogenicity, 80–81  
     genetics, 305*f*, 324–326 (*See also TP53* gene)  
     gene silencing, 317  
     oncogene activation, 301  
     polymorphisms, 269–275, 270*t*

G→T transversions, 303–305, 307  
 mortality, 463  
 risk among former smokers, 676  
 specific carcinogens, 322–324, 323*t*  
 Lung Health Study, 427, 430  
 lymphocyte micronuclei, 79

## M

macular degeneration, 398  
 mainstream smoke, 50–51  
 major depression, 192–193  
 mantle emphysema, 473  
 Marlboro cigarettes, 70  
 Marlboro UltraSmooth cigarettes, 24, 25*t*  
 Massachusetts Department of Public Health, 28  
 Masterpiece Tobacs, 26, 27*t*  
 matches, safety, 18  
 maternal blood pressure  
     acute effects of smoking on, 597*t*–600*t*, 601  
     evidence summary, 635  
     during smoking abstinence, 594, 595*t*, 596  
 maternal cardiovascular system, 594, 595*t*, 596–602, 597*t*–600*t*  
 maternal heart rate  
     acute effects of smoking on, 597*t*–600*t*, 600  
     elevation of, 635  
     during smoking abstinence, 594, 595*t*, 597*t*–600*t*  
 maternal smoking. *See also* fetal effects; reproductive and developmental effects  
     global tobacco epidemic and, 678  
     hormones and, 583  
     later fertility or fecundability, 552  
     tobacco dependence in offspring and, 184  
 matrix metalloproteinases, 515, 515*t*  
 McCarthy Scales of Children's Abilities, 567  
 M cells, 478, 478*f*  
 McLeod syndrome (unilateral form of emphysema), 473  
 mecamlamine, 143, 156, 397  
 mechanisms of action, classification of, 7  
 mechanisms of disease production  
     evidence on, 4, 6*t*, 6–8  
     pathogenicity of tobacco smoke, 3–4  
     schema for, 3–4, 4*f*  
 memory, 150  
 men  
     coronary heart disease in, 384  
     fertility in, 552–553, 554*t*–557*t*  
     hormones, 587, 588*t*–591*t*  
     nicotine dependence prevalence in, 190  
     nicotine reinforcement in, 144  
     relapse risk factors in, 197  
     smoking topography in, 68  
     withdrawal severity in, 142  
 menarche, 551  
 menopause, 551  
 menstrual cycle, 142, 550–551

mentholated smoke, 20, 64–65, 88  
 mercury  
     reproductive and developmental effects, 614–615  
     in tobacco smoke, 60–61, 390, 613  
 Merit cigarettes, 70  
 mesocorticolimbic brain system, 149–150  
 mesolimbic dopamine system, 145, 159–160  
 metabolic activation of carcinogens, 249  
 metals. *See also specific metal*  
     biomarkers, 258  
     reproductive and developmental effects, 613–615, 637  
     in tobacco smoke, 60–61, 390  
 methyllycaconitine, 150, 157  
 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 255*f*, 256  
 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 259, 260*f*  
 methylphenidate, 143  
 micronutrient deficiencies, 625–626  
 microsomal epoxide hydrolase, 270*t*, 274–275  
 Minnesota Child Development Inventory, 567  
 mismatch repair, 282*f*, 282–283  
 modeling of smoking, 203  
 “mode of action,” 7  
 modified tobacco products  
     as alternative to smoking cessation, 71–73  
     cigarette-like products, 17, 27–29, 28*t*  
     harm reduction, 71  
     low-nicotine cigarettes, 24–26, 25*t*, 73  
     modified cigarettes, 23–24, 25*t*  
     nicotine gum (*See* nicotine gum)  
     PREP category (*See* potential reduced-exposure products)  
     regulatory framework for, 34–35  
     smokeless (*See* smokeless tobacco products)  
     tobacco-based lozenges, 22, 26–27, 27*t*, 33  
     types of, 71–73  
 molecular Koch's postulates, 6  
 molecular profiling, 677, 677*f*  
 Monitoring the Future study, 180  
 monoamine oxidase A and B (MAOA and MAOB), 136–137  
 monocytes, 402–403  
 mortality  
     cardiovascular disease, 379  
     COPD, 463, 677–678  
     infant, 564–565, 633  
     lung cancer, 463  
     perinatal, 564–565  
     smoking-related, 15, 673  
     sudden death, 385  
 Motion Picture Association of America, 689  
 motivation as relapse risk factor, 201–202  
 MPOWER Framework (WHO), 679–680  
 MRPs (multidrug-resistance proteins), 487  
 MTT uptake assay, 81  
 mucin, 487  
 mucociliary function, 90–91  
 mucus hypersecretion, 498

multidrug-resistance proteins (MRPs), 487  
 Multinational Study of Vascular Disease in Diabetes, 410  
 Multiple Risk Factor Intervention Trial Research Group, 384  
 mutagen sensitivity assays, 287  
 myelodysplastic syndromes, 80  
 myeloperoxidase, 275  
 myocardial infarction, 383–384  
 myocardial ischemia, 393

## N

*N*-acetylcysteine, 493  
*N*-acetyltransferases (NATs), 265  
 nacystelyn, 493  
 naloxone, 156  
 naltrexone, 148, 153  
 naphthalene, 624  
 nasal cancer, 322, 323*t*  
 nasal spray, nicotine, 137–138, 138*f*, 177–178  
*NAT2* gene, 270*t*, 273–274  
 National Academy of Sciences, 16  
 National Cancer Institute, 687, 691  
 National Comorbidity Survey, 189  
 National Emphysema Treatment Trial, 512  
 National Health Interview Survey, 186, 503  
 National Institute of Mental Health Diagnostic Interview Survey, 186  
 National Institute on Drug Abuse, 25  
 National Institutes of Health (NIH), 16  
 National Longitudinal Study of Adolescent Health, 185  
 National Mortality Followback Survey, 385  
 National Survey on Drug Use & Health, 181, 186  
 Native Americans, 186  
 Nautilus GmbH Laboratoriumsbedarf, 30  
 NDMA (*N*-nitrosodimethylamine), 259, 260*f*  
 “necessary” evidence category, 7  
 neck cancers, 318  
 necrosis, 82  
 negative reinforcement, 142–143, 146, 148  
 “neither necessary nor sufficient” evidence category, 7  
 neonates, hematocrit in, 402  
 nephropathy, 409–410  
 neurochemical correlates of nicotine withdrawal, 151*f*, 156  
 neurodevelopment, 566–567, 580  
 neuronal nicotinic receptors, 165, 168*t*–169*t*  
 neuropathy, 410  
 neutral red incorporation assay, 81  
 Next cigarettes, 16, 25, 73  
 niacin, 414–415  
 nickel  
     reproductive and developmental effects, 614–615  
     in tobacco smoke, 61, 390, 613  
 NicoShot, 30, 31*t*  
 Nicotan, 30, 31*t*

nicotine  
     addictive properties of, 51  
     bioavailability of, 135, 137, 137*t*  
     chemical nature of, 51–54, 52*f*, 53*f*  
     forms of, 53*f*  
     free, 52, 53*f*  
     hemodynamic effects, 392–394  
     metabolism, 139–140, 165, 166*t*–169*t*  
     molecular weight, 135  
     noncarcinogenic, 30  
     reproductive and developmental effects, 612–613  
     significance to tobacco industry, 17  
     structure of, 53*f*  
     as tobacco constituent, 135–137  
 nicotine addiction  
     adolescent sensitivity to, 181  
     components of, 140–148, 145*f*  
     conclusions, 9–10, 207  
     definition and diagnosis, 17, 129–132, 130*t*, 131*t*, 133*t*–134*t*  
     determinants of, 184–185  
     epidemiology of, 186–194, 187*t*–188*t*, 189*f*, 190*t*–191*t*  
     evidence summary, 204–206  
     factors contributing to, 132  
     future research recommendations, 681–683, 682*f*  
     genetics, 161–179, 163*t*–164*t*, 166*t*–177*t*  
     measures of, 133*t*–134*t*  
     medicinal nicotine products and, 138  
     modified cigarettes and, 18  
     pathophysiology of, 148–160, 151*f*  
     prevalence and trajectory of, 180–185  
     reinforcement, 143–144, 145*f*  
         neurosubstrates of, 150–155  
     relapse (*See* relapse)  
     smoking frequency and, 143  
     1988 Surgeon General’s report, 17, 129  
     understanding of, 21, 129  
 nicotine beer, 30, 31*t*  
 nicotine dependence  
     in adolescents, 180–185  
     depression and, 159  
     by dose, duration, and subpopulations, 187*t*–188*t*, 189–191  
     heritability of, 162  
     neurosubstrates of, 151*f*, 155–157  
     prevalence and trajectory toward, 180–185  
     prevalence of, 186–189, 187*t*–188*t*, 189*f*, 190*t*–191*t*  
     psychiatric comorbidity, 191–193  
     schizophrenia, 159–160  
     summary and future directions, 185  
     tolerance to, 140–141  
 nicotine gum  
     for cue-provoked craving, 147–148  
     as PREP, 22  
     rate of nicotine absorption, 138, 138*f*  
     for smoking cessation, 35  
     tobacco-based, 22, 26–27, 27*t*, 33  
 nicotine lollipops, 30, 31*t*  
 nicotine lotion, 30, 31*t*

nicotine lozenges, 22, 26–27, 27*t*, 31, 138  
 nicotine nasal spray, 137–138, 138*f*, 177–178  
 nicotine patch  
   for adolescents, 182  
   cardiovascular disease and, 422*t*  
   for cue-provoked craving, 148  
   pharmacogenetic approach to, 176–178  
   rate of nicotine absorption, 138, 138*f*  
 nicotine replacement therapy (NRT)  
   addiction potential, 138  
   cardiovascular disease and, 420–425  
   harm reduction, 430  
   nontobacco nicotine products, 17, 29–30, 31*t*  
   pharmacogenetic approach, 169, 176–178  
   plasma lipids and lipoproteins, 413  
   pregnancy, 632  
   relapse risk, 200  
 nicotine sunscreen, 29, 31*t*  
 nicotine vapor inhalers, 22  
 nicotine water, 29–30, 31*t*  
 nicotine withdrawal. *See* withdrawal  
 nicotine yield, 19  
 nicotinic acetylcholine receptors  
   airway epithelial cells, 312–313  
   dopamine and, 150  
   nicotine addiction, 149  
 NICO Water, 29, 31*t*  
 NIH (National Institutes of Health), 16  
 nitric oxide  
   as biomarker, 497  
   carcinogenicity, 251  
   reactive oxygen species and, 484–485, 485*f*  
   reproductive and developmental effects, 626  
   vascular effects of, 396, 400–401, 404  
 nitriles, 60  
 nitrogen oxide, 59, 465*t*  
 nitrogen sources, 62  
 nitrosamines, 22, 54–56  
 nitrosamino acids, 255*f*, 256–257  
 NJoy, 31*t*  
 NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), 255*f*, 256  
 N-nitrosamines  
   as biomarkers, 255*f*, 256–258  
   carcinogenicity, 251  
   in tobacco smoke, 54–57, 55*f*  
   types of, 54, 55*f*  
 N'-nitrosoanabasine, 255*f*, 256  
 N'-nitrosoanatabine, 255*f*, 256  
 N-nitrosodimethylamine (NDMA), 259, 260*f*  
 N'-nitrosonornicotine (NNN), 255*f*, 256, 259, 260*f*  
 NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), 259, 260*f*  
 nonenzymatic antioxidants, 486*f*, 487  
 nonhomologous end-joining of DNA, 283, 285*f*  
 nonneoplastic histopathologic changes, 92–93  
 non-small-cell lung cancer, 316–317

nontobacco nicotine products, 17  
 nonvolatile nitrosamines, 54  
 norepinephrine, 154, 156  
 Normative Aging Study, 512  
 nornicotine, 135–136  
 Northern European heritage, people with, 501  
 nortriptyline  
   nicotine addiction and, 159, 674  
   pregnancy and, 632  
   for smoking cessation, 156, 419, 426  
 nose-only exposure, 85  
 1, *N*<sup>2</sup>-propanodeoxyguanosine, 296–297  
 NRT. *See* nicotine replacement therapy  
 NRXN1 gene, 165  
 NRXN3 gene, 165  
 nuclear coronary perfusion studies, 418  
 nuclear factor-kappa B, 311–312  
 nucleotide excision repair  
   overview of, 278–281, 280*f*, 281*t*  
   polymorphisms in the pathway for, 290–291  
   protecting against mutagenicity and carcinogenicity of  
     tobacco carcinogens, 282  
     substrate specificity, 282  
 Nurses' Health Study, 384–385, 407, 410  
 nutrient deficiencies, 625–626

## O

*O*<sup>6</sup>-alkylguanine–DNA alkyltransferase (AGT), 276  
   polymorphisms in, 288  
   protecting against carcinogens, 276  
   substrate specificity, 276  
   in vitro and in vivo studies, 276  
 Obama, Barack, 23  
 Office on Smoking and Health (CDC), 8  
 OGG1 gene, 289  
 olanzepine, 148  
 olefins, 59  
*O*<sup>6</sup>-methyldeoxyguanosine, 296  
*O*<sup>4</sup>-methylthymidine, 296  
 Omni cigarettes, 24, 25  
 oncogenes, 295*t*, 299–301. *See also specific gene*  
 opioid system, 153, 156  
*O*<sup>6</sup>-pyridyloxobutyl-deoxyguanosine, 296  
 oral cancer, 307, 322, 323*t*  
 oral cells and tissues, 268  
 oral premalignant lesions, 80  
 organogenesis, 603–609, 604*t*–608*t*  
 orofacial clefts. *See* cleft lip/cleft palate  
 oviduct (tubal) function, 592, 612, 624, 634  
 ovum (ova), 79  
 oxidants, 488  
 oxidative DNA damage, 80, 257  
 oxidative DNA repair lesions, 75

oxidative stress  
 animal studies, 89  
 antioxidants and, 485–487, 486*f*  
 assessment of, 489, 489*t*, 490*t*, 492*t*–493*t*  
 cell-derived oxidants, 488  
 consequences of, 491, 493–496, 494*t*–495*t*  
 in COPD, 497–500  
 endothelium-dependent vasodilation and, 396–397  
 evidence of, 489–491, 490*t*, 492*t*–493*t*  
 local, 493–495, 494*t*–495*t*  
 platelet function and, 400–401  
 in pulmonary diseases, 520–521  
     central role of, 483  
     summary, 496  
 reactive oxygen species and, 483–485, 484*f*, 485*f*  
 oxidized low-density lipoprotein cholesterol, 403–404  
 oxidizing chemicals, 390  
 8-oxodeoxyguanosine, 296  
 8-oxoguanine DNA glycosylase activity assay, 287

## P

pack-years, 463*n*  
 PAHs. *See* polycyclic aromatic hydrocarbons  
 pancreatic cancer, 268, 322, 323*t*, 324  
 pancreatic juice biomarkers, 75  
 paper, cigarette, 66  
 papillomas, 84  
 paracatricial emphysema, 473  
 paraseptal emphysema, 473  
 particle-size distribution in aerosols, 70–71  
 particulate (tar) phase of tobacco smoke  
     carcinogenic effects, 320–321  
     chemical constituents in, 51  
     defined, 50  
     oxidants in, 488  
     tobacco specific nitrosamines, 55  
 patch. *See* nicotine patch  
 Peabody Picture Vocabulary Test, 567  
 perinatal mortality, 564–565  
 peripheral arterial disease, 386  
 persistent innate and adaptive immune inflammatory response, 479, 480*f*  
 person risk factors for relapse, 195–198  
 PET (positron emission tomography), 136, 158  
*P16* gene, 316  
*P73* gene, 320  
 pH, 53–54, 67  
 pharmacogenetic approaches, 169, 176–179  
 pharmacokinetics of nicotine, 137*t*, 137–140, 138*f*, 139*f*  
 pharmacotherapy for smoking cessation, 419–426, 422*t*–423*t*.  
     *See also* nicotine replacement therapy; *specific drug*  
 phenanthrene metabolites, 254, 255*f*

phenotypes  
     COPD, 502–505, 504*t*  
     of dependence, 132  
     genotype correlations, 291–292  
 Philip Morris Company, 16, 21, 29  
 phosphatidylinositol-3 kinase, 311  
 phosphatidylinositol 3'-phosphatase, 311  
 PHS. *See* Public Health Service  
 Physicians' Health Study, 407  
 Pinkerton Tobacco Company, 26, 26*t*  
 pioglitazone, 415  
 pipes, 386  
 PIs (protease inhibitors), 519, 519*t*  
*PI\*Z* alleles, 501–502  
 placenta  
     biomarkers of exposure, 75  
     blood flow to, 595*t*, 596*t*, 597*t*–600*t*, 602  
     DNA adducts in, 268  
     effects of smoking on, 592–594  
     normal development, 592  
 placental abruption, 561, 636  
 placenta previa, 561, 636  
 plasma-associated lipid transfer enzymes, 412  
 plasmin, 403  
 platelets, impact of smoking on, 399–402, 400*f*  
 polonium, 61, 251  
 polycyclic aromatic hydrocarbons (PAHs), 57  
     as biomarkers, 254, 255*f*, 415  
     carcinogenicity, 251  
     defined, 615  
     developmental effects, 616*t*–621*t*, 622–624  
     endocrine disruption by, 624  
     formation and toxicity, 615  
     in tobacco smoke, 57, 58*f*, 390  
     toxic effects, 624  
 polymorphonuclear leukocytes, 402  
 positive reinforcement, 142–143, 145–146, 148  
 positron emission tomography (PET), 136, 158  
 postprandial hypertriglyceridemia, 409  
 postprandial lipid changes, 413  
 potential reduced-exposure products (PREPs)  
     categories of, 17  
     as cigarette substitutes, 17–18  
     harm reduction, 431, 675  
     regulation of, 33  
     risk assessment, 34  
     types of, 22  
 PPROM (preterm premature rupture of membranes), 563, 636  
 P21 protein, 319  
 P53 protein, 309*f*, 309–310  
 preeclampsia, 560–561, 593, 610–612, 635  
 pregnancy  
     exposure to secondhand smoke during, 678  
     smoking during (*See* maternal smoking)  
 pregnancy complications. *See specific complication*  
 Premier cigarettes, 20, 27–28, 28*t*  
 PREPs. *See* potential reduced-exposure products

President's Cancer Panel, 678–679, 690–692  
 preterm delivery  
   categories of, 562  
   genetic polymorphisms and, 627–631, 630*t*–631*t*  
   secondhand smoke and, 562  
   smoking-related causes, 562–563, 636  
 preterm premature rupture of membranes (PPROM), 563, 636  
*Primary Malignant Growths of the Lungs and Bronchi*, 680  
 product evaluation, 15  
 progesterone, 613  
 prostacyclin, 404  
 Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial, 326  
 protease-antiprotease imbalance, 498, 521  
 protease inhibitors (PIs), 519, 519*t*  
 proteases, 516–520, 518*t*, 519*t*  
 protein adducts, 75, 269  
 protein kinase A, 315  
 protein kinase B (AKT), 311, 314–315  
 protein kinase C, 315  
 protein-signaling pathways, 310*f*, 312  
 psychiatric comorbidity  
   nicotine dependence and, 159–160, 191–193  
   nicotine withdrawal and, 158–159  
   summary and future directions, 160  
 psychiatric dimension, 197–198  
 psychopathology, 184–185  
 Public Health Service (PHS)  
   cardiovascular disease study, 419  
   maternal smoking study, 632  
   nortriptyline study, 159  
   smoke exposure and disease risk study, 19  
 pulmonary defenses, 465–466, 466*f*, 467*f*  
 pulmonary diseases. *See also specific disease*  
   assessment of changes in, 463–464  
   chemicals likely to cause, 49  
   conclusions, 11, 522  
   dosimetry of tobacco smoke and, 465*t*, 465–466, 466*f*, 467*f*  
   evidence summary, 520–521  
   future research recommendations, 684  
   genetics of, 501–513, 504*t*, 506*t*–513*t*, 521  
   implications, 522  
   inflammation in, 498–499  
   nonmalignant, 463, 464*t*, 465*t*  
   overview of, 466  
   oxidative stress and, 483–496, 484*f*–486*f*, 489*t*, 490*t*, 492*t*–495*t*  
   summary, 520  
 pulmonary hypertension, 473–475  
 pyrolysis environment, 67

## Q

Quest cigarettes, 25*t*, 25–26, 73  
 Quick Test Five, 29–30, 31*t*  
 quinapril, 398

## R

racial stock, 385. *See also specific race*  
*RAD23B* gene, 291  
 radioactive elements, 61  
 RAS/mitogen-activated protein kinase, 311  
 Raven Progressive Matrices Test, 567  
 reactive oxygen species (ROS), 483–485, 484*f*, 485*f*, 488  
 reboxetine, 154  
 red blood cells, 401–402  
 regulation, 633–634, 688–690  
   modified cigarettes and substitutes, 17, 33–34  
 reinforcement  
   acute measures of, 143–144  
   defined, 142  
   individual differences in, 144  
   negative, 142–143, 146, 148  
   nicotine *versus* smoking, 144  
   positive, 142–143, 145–146, 148  
   primary, 143  
   secondary, 143  
   smoking frequency and, 143  
 relapse  
   defined, 194  
   influences on, 202*f*, 203  
   lapse-relapse relationship, 195  
   likelihood of, 194  
   natural history of, 194–195  
   negative reinforcement and, 148  
   prevalence of, 194–195  
   rapidity of, 195  
   risk factors for (*See risk factors for relapse*)  
   summary and future directions, 204  
   transition to recovery, 203–204  
 relative risk, 379–380, 380*f*  
 reproductive and developmental effects, 549, 563–580. *See also birth defects; fetal effects; maternal smoking; specific substance or system*  
   biomarkers, 77, 93–96  
   conclusions, 11, 638  
   cytotoxicity, 93–96  
   epidemiology of, 550–580, 554*t*–557*t*, 558*t*–559*t*  
   evidence summary, 634–637  
   future research recommendations, 684–686  
   genotoxicity, 79  
   implications, 632–634  
   studies of, 93–96  
 research, tobacco industry, 19  
 research recommendations  
   cancer, 6–7, 683  
   cardiovascular diseases, 683–684  
   Centers for Disease Control and Prevention, 687  
   future, 674, 681–686, 682*t*  
   nicotine addiction, 681–683, 682*f*  
   pulmonary diseases, 684  
   reproductive and developmental effects, 684–686



respiratory defense mechanisms, 476*f*, 476–483, 478*f*, 480*f*, 481*f*, 482*f*  
 adaptive, 476*f*, 478*f*, 478–479, 480*f*  
 innate, 476*f*, 477–478  
 summary, 482–483  
 tissue remodeling, 479–482, 480*f*, 481*f*, 482*f*  
 respiratory diseases. *See also* pulmonary diseases; *specific disease*  
 animal studies, 90–93  
 biomarkers of, 76–77  
 causal conclusions on, 463, 464*t*  
 nonmalignant, 463, 464*t*, 465*t*  
 retail sales, regulation of, 688–689  
 retinoblastoma protein, 310  
 retinopathy, 410  
 Revel, 26–27, 27*t*  
 reward, 142  
 rimonabant, 154  
 risk assessment tools, 73  
 risk factors for relapse  
 emergent processes, 195, 198–202, 199*f*, 200*f*, 201*f*, 202*f*  
 influences on, 195  
 integration across relapse influences, 202*f*, 203  
 person factors, 195–198  
 situational instigators, 195, 202–203  
 summary and future directions, 204  
 R.J. Reynolds Tobacco Company, 20, 27, 28*t*, 28  
 ROS (reactive oxygen species), 483–485, 484*f*, 485*f*, 488  
 rosiglitazone, 415  
 Ruyan, 30, 31*t*

## S

*Safe and Drug-Free School Act*, 687  
 safety matches, 18  
 saliva biomarkers, 74  
*Salmonella* mutagenicity assay, 76–78  
 SCE (sister chromatid exchange), 78–79  
 schizophrenia, 158–160  
 secondary reinforcement, 144–145, 145*f*  
 secondhand smoke  
 cardiovascular disease and, 387–388  
 diseases linked to, 673  
 dose-response relationship, 381–382  
 during pregnancy, 557, 562, 564, 630*t*–631*t*, 631  
 thrombogenic effects of, 405  
 seminal fluid biomarkers, 75  
 sensitization, 140  
 sensory-gating deficits, 160  
 serotonergic system, 168, 174*t*–175*t*  
 serotonin, 136, 153–154, 156  
 S & F Garret, 30  
 sidestream smoke, 50–51  
 SIDS (sudden infant death syndrome), 565  
 signaling cascades, 316

signal transduction, 308–312, 309*f*, 310*f*  
 sister chromatid exchange (SCE), 78–79  
 situational instigators, 195, 202–203  
 skeletal muscle mass, 499–500  
 skin-painting studies, 83–85  
 Skoal Bandits, 26  
 small airway obstruction, 470, 471*f*  
 small-cell lung cancer, 316–317  
 smoke. *See* cigarette smoke  
 smokeless tobacco products, 26, 27*t*  
 blood levels over time, 137–138, 138*f*, 139*f*  
 cardiovascular disease and, 387  
 consumer perception of, 32  
 harm reduction, 431  
 nitrosamine levels in, 22  
 smoking  
 characteristics of, 67–71  
 compensatory patterns, 19, 21  
 frequency of, 143  
*versus* nicotine reinforcement, 144  
 reduced, as harm reduction, 426–431, 428*t*–429*t*  
 regulations and policies, 633–634  
 trajectory from adolescence to adulthood, 182–184  
 smoking cessation  
 and cancer risk, 250  
 cardiovascular disease and, 383–384, 419–426  
 clinical approach to, 674  
 cost savings with, 633  
 and emphysema progression, 514  
 lapse in (*See* relapse)  
 pharmacotherapy for, 419–426, 422*t*–423*t* (*See also* nicotine replacement therapy; *specific drug*)  
 public health approach to, 674  
 services providing, 692  
 survival curves, 675–676, 676*f*  
 smoking initiation, 148, 161–162  
 smoking machines, 82  
 smoking persistence, 148, 162  
 smoking prevention, 632–633  
 snuff, 387  
 SOD (superoxidase dismutase), 485–486, 486*f*  
 sperm, 79, 268, 625  
*S*-phenylmercapturic acid, 255*f*, 257  
 spontaneous abortion, 553, 556–557, 558*t*–559*t*, 635  
 squamous cell carcinoma, 22, 84  
 St. Louis Alpha-1-Antitrypsin Study, 502  
 STARCURE™ tobacco, 24, 27  
 Star Scientific Company, 24, 27, 27*t*  
 stomach tissue, 268  
 stroke, 385, 611  
 sudden death, 385  
 sudden infant death syndrome (SIDS), 565  
 “sufficient” evidence category, 7  
 sulfur-containing gases, 59  
 sunscreen, nicotine, 30, 31*t*  
 superoxidase dismutase (SOD), 485–486, 486*f*

Surgeon General's report (1964)  
 causal links, 463  
 disease risk, 19  
 low birth weight, 564  
 mechanism of disease production, 4, 6*f*  
 smoking and health, 3, 673, 680  
 Surgeon General's report (1979), 3  
 Surgeon General's report (1981), 19, 21  
 Surgeon General's report (1982), 4, 6  
 Surgeon General's report (1986), 3  
 Surgeon General's report (1988)  
 drug dependence criteria, 129–130  
 nicotine addiction, 17, 129, 204  
 Surgeon General's report (1990), 419  
 Surgeon General's report (2000), 3, 680  
 Surgeon General's report (2001)  
 fertility, 552, 634  
 low birth weight, 564  
 menopause, 551  
 perinatal mortality, 565  
 reproductive hormones, 581, 583  
 Surgeon General's report (2004)  
 causal links, 249, 464*t*  
 evidence strength, classification levels, 7  
 female fertility, 634  
 low birth weight, 564  
 male fertility, 552  
 maternal smoking, 565, 567  
 mechanism of disease production, 6  
 passive smoking, 3  
 pregnancy complications, 556–557, 560–561, 563, 636  
 sudden infant death syndrome, 565  
 Surgeon General's report (2006)  
 causal links, 464*t*  
 passive smoking, 3  
 secondhand smoke, 379, 387, 557, 562, 564, 679  
 Swedish Match Company, 26–27  
 sympathetic nervous system, 388–389, 390, 391*f*, 392, 393, 394, 411  
 synergistic interactions in carcinogenesis, 321–322  
 systemic oxidative stress, 495

## T

tar delivery, 18, 21, 62  
 target populations, 19–20  
 tar phase of tobacco smoke. *See* particulate (tar) phase of tobacco smoke  
 tar yield, 19  
 taxes, cigarette, 680  
 T cells, 478*f*, 479  
 testing standards, 49  
 test methods  
*versus* actual smoking, 67  
 chemistry and toxicology, 49  
 FTC, 21–22  
 for tar yields, 19

TGF- $\alpha$ , 313–314  
 thallium, 61  
 thioredoxin (Trx) system, 487  
 Third National Health and Nutrition Examination Survey, 580  
 Thompson, Tommy G., 24  
 thrombogenic effects  
 nicotine, 405  
 risk factors for, 399  
 secondhand smoke, 405  
 summary, 406  
 thrombosis, 395  
 thromboxane A<sub>2</sub>, 90, 415  
 timing of emergent processes, 201*f*, 201–202, 202*f*  
 tissue factor, 395, 404–405  
 tissue plasminogen activator, 405  
 tissue remodeling, 479–482, 480*f*, 481*f*, 482*f*  
 tobacco  
 alkaloids, 51–52, 52*f*  
 constituents and pharmacokinetics, 135–140, 137*t*, 138*f*, 139*f*  
 cut widths, 66  
 harm-reduction strategies, 15  
 heating systems, 71–72  
 processing and nitrosamine formation, 54  
 types of, 55–57, 65–66  
 tobacco-based lozenges, 22, 26–27, 27*t*, 31  
 tobacco control measures, 686–688  
 tobacco epidemic, global, 673–678, 676*f*, 677*f*  
 ending, 678–680  
 tobacco industry, 19, 691  
 tobacco smoke. *See also* cigarette smoke  
 carcinogenic effects of, 320–321  
 characteristics and components of, 464–465, 465*t*  
 characteristics of, 465*t*  
 dosimetry of, 465*t*, 465–466, 466*f*, 467*f*  
 phases of, 50–51  
 tobacco-specific nitrosamines (TSNAs)  
 curing process, 72  
 delivery to smokers, 67–68  
 filter tips, 56  
 modified tobacco products, 23, 27  
 particulate phase of tobacco smoke, 55  
 testing for, 56  
 types and structure of, 54, 55*f*  
 tolerance, 140–141  
 TP53 gene, 302–307  
 cancer associations, 302*f*, 302–303, 304*f*, 305*f*, 306*f*, 307  
 cell-cycle control, 319  
 cytogenicity and, 80–81  
 G→T transversions, 303–305  
 study limitations, 307  
 transcription-coupled repair, 281–282  
 transdermal system. *See* nicotine patch  
 translesion synthesis, 293, 294*f*, 294*t*, 295  
*Treating Tobacco Use and Dependence: Clinical Practice Guidelines* (PHS), 419  
 Trx (thioredoxin) system, 487

TSNAs. *See* tobacco-specific nitrosamines  
 tubal (oviduct) function, 592, 612, 624, 643  
 tumor-suppressor genes  
     identification of, 298*t*, 298–299  
     in lung cancer, 298*t*, 299, 301  
     regulation of, 308–310, 309*f*

## U

uncharacterized adducts, 268  
 unconditioned stimulus, 144–145, 145*f*  
 unilateral form of emphysema (McLeod syndrome), 473  
 United Kingdom Prospective Diabetes Study, 410  
 University of Minnesota Transdisciplinary Tobacco Use Research Center, 33  
 upper aerodigestive tract cancer, 80  
 uridine-5'-diphosphate-glucuronosyltransferases, 264–265  
 urinary biomarkers  
     biologically effective dose, 75–76  
     carcinogens, 254–258, 255*f*  
     exposure, 74  
     potential harm, 76  
 U.S. Lung Health Study, 469, 678  
 U.S. Smokeless Tobacco Company, 26  
 U.S. Tobacco Use and Dependence Guideline Panel, 679  
 uterine blood flow, 595*t*, 596*t*, 597*t*–600*t*, 602

## V

vapor inhalers, nicotine, 22  
 varenicline  
     pharmacogenetic approach, 178  
     pregnancy, 632  
     for smoking cessation, 419, 426, 674  
 vascular homeostasis, 396  
 vasoconstriction, coronary, 392–394  
 vasodilation, 396, 415  
 ventilated filters  
     blocking of holes by smokers, 69  
     in cigarette filters, 20  
     delivery of chemicals into smoke, 67  
     lung adenocarcinomas and, 22  
 vigabatrin, 152  
 Virchow's triad, 399  
 vitamin absorption, 77  
 vitamin C  
     biomarkers of oxidative damage, 258  
     deficiencies of, 625  
     endothelium-dependent vasodilation and, 397  
     monocytes, 402  
     nonenzymatic antioxidant, 487

vitamin E, 487  
 volatile compounds, 58–60  
 volatile nitrosamines, 54–56  
 von Willebrand protein, 395, 404

## W

water, nicotine, 29–30, 31*t*  
 waterpipe smoking, 33–34  
 Wechsler Preschool and Primary Scale of Intelligence - Revised, 567  
 weight. *See* birth weight; body weight  
 WHO. *See* World Health Organization  
 whole-body exposure, 85  
 withdrawal  
     in adolescents, 182  
     antidepressant and antipsychotic drugs for, 158–159  
     individual differences in, 142  
     molecular mechanisms of, 157–158  
     platelet MAO activity and, 137  
     relapse risk factors, 199*f*, 199–200, 200*f*, 201*f*  
     symptoms of, 141–142  
 women  
     cigarette marketing to, 19  
     coronary heart disease in, 384  
     effect of smoking on, 581–586, 584*t*–587*t*, 592–594  
     fertility, 552  
     nicotine dependence prevalence in, 190  
     nicotine reinforcement in, 144  
     relapse risk factors in, 197  
     smoking topography in, 68  
     withdrawal severity in, 142  
 World Health Organization (WHO)  
     on causes of death, 673  
     Framework Convention on Tobacco Control, 23–24  
     MPOWER Framework, 679–680  
     nortriptyline study, 159  
     questions and recommendations for new products, 33  
     tobacco harm reduction, 16

## X

xeroderma pigmentosum A (XPA), 290  
 xeroderma pigmentosum C (XPC), 290  
 xeroderma pigmentosum complementation group D (XPD), 290–291  
*XPF/ERCC1* gene complex, 291  
*XPG/ERCC5* gene complex, 291  
*XRCC1* (cross-complementation group 1 for excision repair), 288–290